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| 10/552,299 | 08/25/2006 | Orit Kollet | 30694/41506 | 2069 |

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| EXAMINER | |
|---|---|
| SHEN, WU CHENG WINSTON | |

| ART UNIT | PAPER NUMBER |
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| 1632 | |

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| 10/14/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/552,299 | KOLLET ET AL. | |
| | Examiner | Art Unit | |
| | WU-CHENG SHEN | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 August 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

5)☒ Claim(s) *1-62* is/are pending in the application.

5a) Of the above claim(s) *8,10-29,37 and 40-62* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7,9,30-36,38 and 39* is/are rejected.

8)☒ Claim(s) *1-7 and 9* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *07 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claim set filed on 08/01/2011 has been entered. Applicant's arguments filed on 08/01/2011 have been entered.

Applicant's summary of interview field on 08/17/2011 has been entered. Pertaining to Examiner's interview summary mailed on 08/03/2011, it is noted that "SDF-1" was a typographic error of "SCF" stated in the second to the last sentence "Kollet et al. teaches that the expression of CXCR4 is increased in the hematopoietic stem cells during the process of hematopoietic stem cells mobilization from bone marrow upon induction by chemoattractant **SCF**". For the clarity of record, it is noted that SCF is a cytokine stands for "stem cell factor", which is a ligand of receptor c-kit (sKitL, soluble Kit-ligand). SDF-1 is a chemokine stands for "stromal cell-derived factor-1", which is a ligand for receptor CXCR4. Further elaboation in this regard is provided in the 103(a) rejection documneted in this offcie aciton.

This application 10/552,299 filed on 08/25/2006 is a 371 of PCT/IL04/00314 filed on 04/07/2004, which claims the benefits of foreign applications ISRAEL 155302 filed on 04/08/2003 and ISRAEL 159306 filed on 12/10/2003.

### *Election/Restriction*

The following statements have been documented in the Non-Final office action mailed on 03/01/2011.

In response to revised Restriction/Election mailed on 11/12/2010, Applicant's election with traverse of Group IX, drawn to claims 1-7, 9 (in part, pertaining to increasing level of chemoattractant receptor CXCR4 of the stem cells), 30-36, 38, and 39, drawn to a method of

generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation, in the reply filed on 12/10/2010 is acknowledged.

The traversal is on the ground(s) that Applicant incorporates the arguments found in the response filed March 6, 2009 to traverse the restriction requirement. The traversal is not found persuasive for the reasons documented on pages 2-3 of the office action mailed on 05/27/2009. With regard to election of species, as documented on pages 3-4 of the office action mailed on 05/27/2009, upon further consideration, the requirement for election of species between MMP-2 and MMP-9 recited in claim 33 is withdrawn because further search indicates that MMP-2 and MMP-9 are obvious variants to each other (See, for instance, **Skiles et al.**, The design, structure, and clinical update of small molecular weight matrix metalloproteinase inhibitors, *Curr Med Chem.* 11(22):2911-77, 2004).

Claims 1-62 are pending. Claims 8, 10-29, 37, and 40-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-7, 9, 30-36, 38, and 39, drawn to a method of generating hematopoietic stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for

transplantation are currently under examination to the extent of stem cells being hematopoietic stem cells, are currently under examination.

The requirement is still deemed proper and is therefore made FINAL

### *Claim Objections*

1. Claims 1-7 and 9 are objected to for being drawn to a non-elected invention. Specifically, Applicants have elected Group IX invention as recited in claim 30 and as such, claim 1 and dependent claims 2-7 and 9 are examined only to the extent that they read on an "*In vitro*" method and isolated stem cell having increased "CXCR4". It is worth noting that the *in vivo* aspect of claim 1 and its dependent claims belong to inventions Groups II and IV as documented in the Restriction/Election mailed on 11/12/2010. Applicants are required to amend the claims to delete the non-elected subject matter from the instant claim 1 and its dependent claims.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Previous rejection of claims 1-7, 9, 30-36, 38, and 39 under 35 U.S.C. 103(a) as being unpatentable over **Rafii et al.** (US 2004/0071687, publication date 04/15/2004, filed on 05/28/2003, provisional application 60/383,658 filed on 05/28/2002) in view of **Fisher et al.**

(Fisher et al., Engineering autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse brain, *Biochemistry* 41(26):8289-97, 2002), **Möhle et al.** (Möhle et al.,The chemokine receptor CXCR-4 is expressed on CD34+ hematopoietic progenitors and leukemic cells and mediates transendothelial migration induced by stromal cell-derived factor-1, *Blood* 91(12): 4523-30, 1998) and **Kollet et al.** (Kollet et al., Rapid and efficient homing of human CD34(+) CD38(/low) CXCR4(+) stem and progenitor cells to the bone marrow and spleen of NOD/SCID and NOD/SCID/B2m(null) mice, *Blood* 97(10):3283-91, 2001; this reference is listed as reference C35 in the IDS filed by Applicant on 01/29/2007) is ***withdrawn*** because upon further consideration, further revisions of the 103(a) rejection should be documented for the clarity of 103(a) rejection.

3. Claims 1-7, 9, 30-36, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Rafii et al.** (US 2004/0071687, publication date 04/15/2004, filed on 05/28/2003, provisional application 60/383,658 filed on 05/28/2002) in view of **Lapidot et al.** (Lapidot et al. Mechanism of human stem cell migration and repopulation of NOD/SCID and B2mnull NOD/SCID mice. The role of SDF-1/CXCR4 interactions, *Ann N Y Acad Sci.* 938:83-95, 2001) and **Fisher et al.** (Fisher et al., Engineering autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse brain, *Biochemistry* 41(26):8289-97, 2002).

Claims 1 and 2 are directed to a method of increasing sensitivity of stem cells to a chemoattractant, the method comprising exposing the stein cells to a matrix metalloprotease or an active portion thereof, which is capable of increasing a level of at least one chemoattractant receptor of the stem cells to thereby increase the sensitivity of the stem cells to the chemoattractant, wherein said at least one chemoattractant receptor is CXCR4.

Claims 3 and 4 is recited to the method of claim 1, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

Claim 5 is directed to the method of claim 1, wherein the stern cells are hematopoietic stem cells.

Claim 6 is directed to the method of claim 5, wherein said hematopoietic stein cells are CD34+ hematopoietic stem cells.

Claim 7 is directed to the method of claim 6, wherein said hematopoietic stern cells are $CD34^{+}/CD38^{-/low}$ hematopoietic stem cells.

Claim 9 is directed to the method of claim 1, wherein said exposing the stem cells to said matrix metalloprotease or said active portion thereof; is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or an active portion thereof in the stem cells; and/or (ii) contacting the stem cells with said matrix metalloprotease or an active portion thereof.

Claim 30 is directed to a method of generating stem cells suitable for transplantation, the method comprising: (a) collecting stem cells; (b) exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof; and (c) isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof, to thereby generate stem cells suitable for transplantation.

Claim 31 is directed to the method of claim 30, wherein collecting said stem cells is effected by: (i) a stem cell mobilization procedure; and/or (ii) a surgical procedure.

Claim 32 and 33 are directed to the method of claim 30, wherein said matrix metalloprotease is selected from the group consisting of MMP-2 and MMP-9.

Claim 34 is directed to the method of claim 30, wherein said stem cells are hematopoietic stem cells.

Claim 35 is directed to the method of claim 34, wherein said hematopoietic stem cells are CD34+ hematopoietic stem cells.

Claim 36 is directed to the method of claim 34, wherein said hematopoietic stem cells are $CD34^{+}/CD38^{-/low}$ hematopoietic stem cells.

Claim 38 is directed to the method of claim 30, wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof`, is effected by: (i)

expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof.

Claim 39 is directed to the method of claim 30, wherein said isolating stem cells having increased CXCR4 levels compared to stem cells not exposed to the matrix metalloprotease or an active portion thereof is effected by FACS.

*Claim interpretations*: The limitation "increasing a level of at least one chemoattractant receptor of the stem cells" recited in claim 1 encompasses CXCR4 recited in claim 2 and any other chemoattractant receptor expressed in the claimed stem cells. More discussions have been stated in the "***Claim Objections***" section in this office action, and the teachings of Rafii et al. and Lapidot et al. discussed in this 103(a) rejection.

With regard to limitation "collecting stem cells" recited in step (a) of claim 30 and the limitations of claim 39, **Rafii et al.** teaches that protease play a key role in recruiting stem cells from a quiescent state to proliferate and differentiate (See paragraph [0009], summary of the invention, Rafii et al., 2004). Rafii et al. teaches that the stem cells can be hematopoietic stem cells, endothelial stem cells, hepatic stem cells, neuronal stem cells, muscle stem cells or a combination thereof. The quiescent non-cycling stem cells are often in contact with bone marrow stromal cells, including osteoblasts and/or are generally maintained in a $G_0$ phase of cell cycle. The quiescent non-cycling stem cells can be $Lin^-Sca^+c\text{-}Kit^+$ hematopoietic stem cells, $VEGFR2^+c\text{-}Kit^+$ endothelial stem cells, $VEGFR2^+$ vascular stem cells or $AC133^+$ organ-specific stem cells (See paragraph [0017], Rafii et al., 2004). Rafii et al. teaches that S-phase $Lin^-Sca\text{-}1^+c\text{-}Kit^+$ stem cells, isolated by a combination of magnetic cell isolation (MACS) and *flow cytometry (FACS)* (See paragraph [0027], Rafii et al., 2004).

Pertaining to the limitation "exposing said stem cells to an exogenous matrix metalloprotease or an active portion thereof" recited claim 1 and in step (b) of claim 30, the limitation "wherein said exposing said stem cells to said exogenous matrix metalloprotease or said active portion thereof, is effected by: (i) expressing a polynucleotide encoding said matrix metalloprotease or said active portion thereof in said stem cells; and/or (ii) contacting said stem cells with said matrix metalloprotease or said active portion thereof" recited in claims 9 and 38, **Rafii et al.** (US 2004/0071687) teaches endothelial-active cytokines, such as VEGF, and SDF-1 and their role in inducing mobilization of bone marrow repopulating cells, and MMPs are necessary intermediates downstream of these factors. Cytokine-induced mobilization of hematopoietic progenitors and cells with hematopoietic stem cell potential was markedly impaired in MPI-treated or MMP-$9^{-/-}$ mice (See paragraph [0107], US 2004/0071687). Rafii et al. teaches that bone marrow cells as compositions can be cultured in the presence of growth factor/cytokine SCF (c-kit ligand), chemokine SDF-1 prior to administration to an animal (See paragraph [0145], Rafii et al.). Rafii et al. further teaches that MMP-9 promotes *release of stem cell active cytokines*, thereby promoting expansion of quiescent stem cells, and this novel concept lays the foundation of developing strategies where *activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells* that may ultimately be used for organ-regeneration and tissue vascularization (See paragraph [0114], and Figure 16, shown below, US 2004/0071687). In this regard, Rafii et al. demonstrated that *MMP-9-mediated release of sKitL (soluble Kit-ligand) is essential for promoting stem cell differentiation, accelerating hematopoietic reconstitution following bone marrow ablation* (See paragraph [0197] and Figure 16 provided below, US 2004/0071687). Rafii et al. teaches that *exogenous*

*sKit-L (soluble Kit-ligand) restores hematopoietic recovery and mobilization* in MMP-9-/- mice (See paragraph [0195], US 2004/0071687), and *SCF is the c-Kit ligand* (See paragraph [0145], US 2004/0071687).

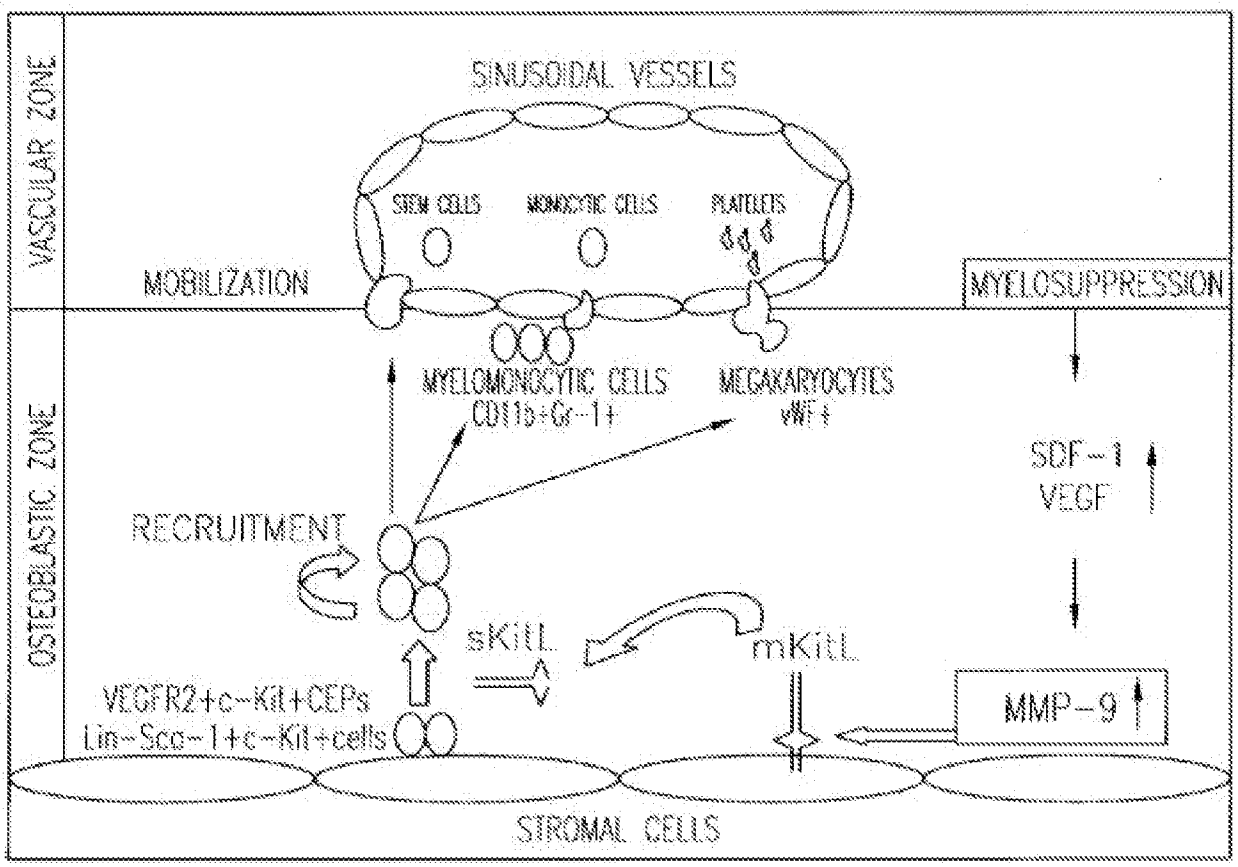


**FIG. 16**: a schematic diagram of the recruitment process. Under steady-state conditions quiescent c-Kit$^+$ hematopoietic stem cells and CEPs reside in a niche in close contact with stromal cells, including osteoblasts. Membrane-bound cytokines such as mKitL not only convey survival signals, but also support the adhesion of stem cells to the stroma. Bone marrow ablation or chemokine/cytokine administration induces up-regulation of MMP-9 resulting in the release of sKitL (soluble Kit-ligand). sKitL provides signals that enhances mobility of VEGFR2$^+$ endothelial progenitors (CEPs) and Lin$^-$Sca-1$^+$c-Kit$^+$ repopulating cells, translocating them into a vascular-enriched niche favoring differentiation and mobilization to the peripheral circulation.

Pertaining to the expression of a polynucleotide encoding a gene of interest in stem cells recited in claim 38, Rafii et al. teaches that *in vivo* gene transfer using a biological means can be accomplished by administering the virus containing the DNA to the mammalian subject either by an oral route, or by injection depending upon the tissue targeted for gene transfer. For example, where the targeted cells are *stem cells* and where a virus containing the DNA of interest is administered into the bone marrow, the virus will be administered at a concentration effective to infect *bone marrow cells* of the mammalian subject and provide for expression of the nucleic acid sequence at levels sufficient to recruit stem or progenitor cells from the bone marrow (See paragraph [0130], US 2004/0071687). It is worth noting that Rafii et al. teaches that bone marrow not only provides a suitable micro-environment for hematopoietic stem cells, but is also a dispensable reservoir for organ-specific stem cells for endothelium, muscle, brain, pancreas, and liver cells (See paragraph [0109], US 2004/0071687).

Rafii et al. does not *explicitly* teach the limitation **(i)** stem cell having increased CXCR4 level recited in claim 30 and claim 2, and the limitation **(ii)** hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells recite din claim 36 and claim 7, and the limitation **(iii)** the expression of exogenous MMP protein from a polynucleotide or addition of exogenous matrix matalloproteiase (MMP) or active portion thereof, as recited in claims 38 and claim 9.

However, at the time of filing of instant application, the limitation **(i)** stem cell having increased CXCR4 level recited in claim 30 and claim 2, and the limitation **(ii)** hematopoietic stem cells are CD34+/CD38-/low hematopoietic stem cells recite din claim 36 and claim 7, and the limitation **(iii)** the expression of exogenous MMP protein from a polynucleotide or addition

of exogenous matrix matalloproteiase (MMP) or active portion thereof, as recited in claims 38 and claim 9 were know in art.

With regard to **(i)-(ii), Lapidot et al. (2001)** teaches that the mechanism of hematopoietic stem cell migration and repopulation is not fully understood. Murine fetuses that lack the chemokine stromal-derived factor one (SDF-1null) or its receptor CXCR4 (CXCR4null) have multiple defects that are lethal, including impaired bone marrow hematopoiesis. These results suggest a major role for SDF-1/CXCR4 interactions in murine stem cell homing from the fetal liver into the bone marrow and its repopulation during development. SDF-1 is highly conserved between different species. Human and murine SDF-1 are cross-reactive and differ in one amino acid. Lapidot et al. (2001) reported that SDF-1 and CXCR4 are essential for homing and repopulation of immune-deficient NOD/SCID and B2mnull NOD/SCID mice by human stem cells. In addition, immature human CD34+ cells and primitive CD34+/CD38-/low cells, which do not migrate toward a gradient of SDF-1 *in vitro*, and do not home and repopulate *in vivo* the murine bone marrow, can become functional repopulating cells by short-term 16-48 hr *in vitro* stimulation with cytokines such as SCF and IL-6 prior to transplantation. These cytokines ***increase surface CXCR4 expression****, migration toward SDF-1, and in vivo homing and repopulation*. Lapidot et al. discuss the pleiotropic roles of SDF-1/CXCR4 interactions in human stem cell migration, development, and repopulation in transplanted immune-deficient mice (See abstract, page 83, Lapidot et al., 2001). Lapidot et al. further teaches that SDF-1 was also found to mediate the migration of immature human CD34+ cells across bone marrow blood vessels subendothelial basement membranes *by regulating production of matrix-degrading metalloproteinases (MMPs) MMP2 and MMP9.* These enzymes which are *produced by*

*hematopoietic*, endothelial, and epithelial cells participate in homing and release of hematopoietic cells which require penetration across the blood endothelium and bone marrow stroma by degrading all the components of the ECM (extracellular matrix) (See page 85, Stem cell homing and repopulation, Lapidot et al., 2001). With regard to "isolating stem cells having increased CXCR4" recited in step (c) of claim 30, Lapidot et al. teaches sorting of various CD34+ cells subpopulations based on expression of CXCR4 (See page 87, Lapidot et al., 2001).

Based on the combined teachings of Rafii et al. and Lapidot et al. increased endogenous production of MMP-9 by hematopoietic stem cells results in release of sKitL (soluble Kit-ligand) which is SCF (c-kit ligand) in the process of hematopoietic stem cell migration and repopulation, and SDF-1/CXCR4 interactions play pleiotropic roles in regulation of human stem cell migration.

With regard to **(iii)** pertaining to *exogenous* MMP-9 recited in claim 30, **Fisher et al.** teaches engineering wild type and various mutant autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse brain to evaluate the effect of increased levels of active MMP-9 in the central nervous system (See title and abstract, Fisher et al., 2002).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Rafii et al. regarding activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells for stem cell recruitment/homing, and MMP-9-mediated release of sKitL (soluble Kit ligand, which is c-Kit ligand, SCF) is essential for promoting stem cell differentiation,

accelerating hematopoietic reconstitution following bone marrow ablation, with the teachings of **(i)** Lapidot et al. regarding SCF increase surface CXCR4 expression, migration toward SDF-1, *in vivo* homing and repopulation, and SDF-1 mediates the migration of immature human CD34+ cells across bone marrow blood vessels subendothelial basement membranes by regulating production of matrix-degrading metalloproteinases (MMPs) MMP2 and MMP9 whereas these enzymes which are produced by hematopoietic, endothelial, and epithelial cells participate in homing and release of hematopoietic cells which require penetration across the blood endothelium and bone marrow stroma by degrading all the components of the ECM (extracellular matrix), and **(ii)** Fisher et al. regarding engineering wild type and various mutant autoactivating forms of matrix metalloproteinase-9 and expression of the active enzyme in cultured cells, to arrive at claimed methods recited in claims 1-7, 9, 30-36, 38, and 39 of instant application, by substitution of endogenous increased expression of MMP-9 in hematopoietic cells, taught by both Rafii et al. and Lapidot et al., with exogenous expression MMP-9 from a polynucleotide, taught by Fisher et al.

One having ordinary skill in the art would have been motivated to combine the teachings of Rafii et al., Lapidot et al. and Fisher et al. because both Rafii et al. and Lapidot et al. teaches the molecular mechanisms of hematopoietic stem cells migration. More specifically, Rafii et al. teaches the MMP-9-mediated release of sKitL (soluble Kit ligand; which is c-Kit ligand, SCF) is essential for promoting stem cell differentiation, accelerating hematopoietic reconstitution following bone marrow ablation whereas Lapidot et al. teaches *in vitro* stimulation of hematopoietic stem cells by SCF (c-Kit ligand) increase surface CXCR4 expression in the hematopoietic stem cells, migration toward SDF-1, *in vivo* homing and repopulation, and the role

of SDF-1/CXCR4 interactions in human stem cell migration. Furthermore, Fisher et al. demonstrated that exogenous expression MMP-9 from a polynucleotide can be introduced in cultured cells.

There would have been a reasonable expectation of success given (i) the establishment of MMP-9 promotes release of stem cell active cytokines, thereby promoting expansion of quiescent stem cells, and activation of MMP-9 may act as molecular switches to expand a large population of stem cells, and the role of cytokine SCF (c-Kit ligand) and chemokine SDF-1 in inducing mobilization of bone marrow repopulating cells, by the teachings of Rafii et al., (ii) the disclosure of stimulation of hematopoietic stem cells by SCF increases surface CXCR4 expression of the stem cells, migration toward SDF-1, *in vivo* homing and repopulation, and SDF-1 mediates the migration of immature human CD34+ cells across bone marrow blood vessels subendothelial basement membranes by regulating production of matrix-degrading metalloproteinases (MMPs) MMP2 and MMP9, and the pleiotropic roles of SDF-1/CXCR4 interactions in human stem cell migration, by the teachings of Lapidot et al., and (iii) successful demonstration of genetic engineering wild type and various mutant auto-activating forms of human matrix metalloproteinase-9 and expression of the active enzyme in cultured cells and transgenic mouse, by the teachings of Fisher et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat.

App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) [available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf; and *KSR Guidelines Update* has been published in the Federal Register at 75 *Fed. Reg.* 53643-60 (Sep. 1, 2010) and is posted at USPTO's internet Web site at http://www.uspto.gov/patents/law/notices/2010.jsp]. The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Rafii et al., Lapidot et al. and Fisher et al. has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

***Applicant's arguments*** and Examiner's ***Response to Applicant's arguments***

Applicant's remarks filed on 08/01/2011 regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above in this office action.

The Examiner notes that Lapidot et al. specifically teaches that stimulation of hematopoietic stem cells by cytokine SCF, the c-Kit ligand taught by Rafii et al., increases surface CXCR4 expression of the stem cells, migration toward SDF-1, and *in vivo* homing and repopulation. Lapidot et al. further teaches that SDF-1 mediates the migration of immature human CD34+ cells across bone marrow blood vessels subendothelial basement membranes by regulating production of matrix-degrading metalloproteinases (MMPs) MMP2 and MMP9 whereas these enzymes which are produced by hematopoietic, endothelial, and epithelial cells participate in homing and release of hematopoietic cells which require penetration across the blood endothelium and bone marrow stroma by degrading all the components of the ECM (extracellular matrix). The teachings by Lapidot et al. are consistent with and complementary to the teachings of Rafii et al. that protease play a key role in recruiting stem cells from a quiescent state to proliferate and differentiate, and that activation of proteases such as MMP-9 may act as molecular switches to expand a large population of stem cells that may ultimately be used for organ-regeneration and tissue vascularization.

Additional prior art that is consistent with the teachings of Lapidot et al., but not listed in the 103(a) rejection documented in this office action, includes **Peled et al.** (Peled et al. Dependence of human stem cell engraftment and repopulation of NOD/SCID mice on CXCR4, *Science* 283(5403):845-8, 1999; this reference has been cited as NPL C57 in the IDS filed by Applicant on 01/29/2007).

***Conclusion***

4. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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Art Unit 1632